Artificial Enzyme Catalyzes Multi-Step Chemical Reaction

Senior Faculty Scientist Jean M. J. Fréchet has developed a new method for catalyzing complex, multi-step reactions in solution. It mimics a common feature of living systems; the ability to spatially isolate the individual reaction centers along the multi-step pathway, while allowing access to each successive center by the product of the previous one.

Living cells often synthesize complex molecules via multistep sequential reactions, each catalysed by an enzyme. To allow all of the reactions to work well, nature uses "compartmentalization" or "site isolation," through which the individual steps are spatially separated to optimize their action. This concept has been adopted for use in solid-state catalysis by, for example, separating reaction centers in different areas of a solid support with the product of the reaction at one center diffusing to the next center for the next reaction. However, site isolation is more challenging in the liquid phase, as the molecules cannot so easily be immobilized.

The key to achieving site isolation in solution lay in the use of "star polymers," macromolecules that are capable of being functionalized so that they can bind and encapsulate small catalytic molecules in their core, adjacent to the binding site for the "reactant." Fréchet's group synthesized a pair of these polymers, each with a specific binding site. The first was designed to bind the starting materials, the second was designed to trap the product of the first reaction and convert it to final product. In a demonstration experiment, they made a star polymer with a core functionalized with a "sulfonate" group, which could immobilize the catalyst imidazolidinone. The two starting materials in the reactant path bind to that site and are converted by the imidazolidinone to an intermediate product. This intermediate product then diffuses to the second star polymer designed to immobilize the second catalyst, a pyrrolidine derivative. There, it is converted to the final product through simultaneous catalysis by the pyrrolidine and a third catalyst, this one in solution. When all three catalysts were present, 90% of the starting material was converted to product, showing that a "cascade" of all reaction steps had occurred. No or very little product was observed with the polymers without the catalysts. Further, the catalysts used in this work were designed to be "chiral," in an attempt to control which mirror image of the product was to be produced. In this experiment, more than 99% of the product had the preferred "chirality." The group further demonstrated that all four possible mirror images of the cascade reaction could easily be made simply by changing the catalyst chirality. (There are two optically active centers in the molecules of this reaction, thus four possible mirror images.)

In summary, proper site isolation with star polymers enables the combined use of otherwise incompatible catalysts for complex asymmetric cascade reactions. This represents the most sophisticated achievement of a multistep chemical process in solution using an artificial enzymatic process.

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Yonggui Chi, Steven T. Scroggins, and Jean M. J. Fréchet, "One-Pot Multi-Component Asymmetric Cascade Reactions Catalyzed by Soluble Star Polymers with Highly Branched Non-Interpenetrating Catalytic Cores," *J. Amer. Chem. Soc.* **130**, 6322–6323 (2008).

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Formation of the chiral reaction product (blue in box, lower line) from three starting materials (lower line extreme left and extreme right) requires the involvement of three separate catalysts (star-iminium, star-enamine and H-bonding). The iminium and enamine catalysts must be kept separated within star polymers to avoid mutual deactivation. The chirality within the stars determines product chirality which was 99% pure in this case. No product is obtained in the absence of site-isolation.